REMARKS

This reply is submitted with a Request for Continued Examination ("RCE"). Upon entry of the present amendments, claims 1-14, 16, 20, 25-36, 38-50, and 52-57 will be pending. Claims 10, 14, 26-36, 38-50, and 52 are withdrawn. Claims 15, 17-19, 21-24, 37, and 51 have been canceled. Applicants have amended claims 1, 3, 4, 26, and 34 to more clearly point out the claimed subject matter. These amendments are supported in the application. For example, the concept of a flat substrate is described in the application, e.g., at page 5, line 22. The concept that the different areas on the substrate can be contacted with one sample at essentially the same time and with the same sample is described throughout the application (see, e.g., page 13, lines 17-19, and page 26, lines 1-3). Applicants have also added new claims 53-57, which are supported by language found in the original claims and throughout the specification. For example, the concept of incubating different areas on the substrate with the same sample simultaneously is described in the specification (see, e.g., at page 26, lines 1-7). The concept of using a bead or quantum dot as a substrate is also described in the specification, for example, at page 5, lines 23-25.

Applicants have also amended the specification to refer to various "CY" dyes as trademarks as requested by the Office. No new matter has been added.

Interview Summary

Applicants thank Examiner Jung for a telephone interview on March 24, 2008 with applicants' representatives to discuss the Office Action dated December 27, 2007.

Applicants' representatives noted that the specification would be amended to address the objection regarding the use of the various "CY" trademarks.

With respect to the obviousness rejections, applicants' representatives noted that the Office Action does not address how the cited references suggest an array having a plurality of spatially-distinct areas that are configured to allow incubation of all the areas essentially at the same time with the same sample, as now recited in the claims. The Examiner acknowledged that the references are silent on these recited elements. However, the Examiner suggested that these are merely functional, rather than structural limitations, and therefore, were not considered in

determining the patentability of the claims. Applicants' representative suggested amending the claims to point out that the recited array is flat to distinguish it from, for example, microtiter plates. The Examiner stated that such amendment might possibly differentiate the instant claims from the cited references, but would not be entered given that this is a final office action.

Information Disclosure Statement

Applicants thank the Examiner for making the required corrections to the Form PTO-1449 as noted at page 2 of the Office Action.

Withdrawn Objections and Rejections

Applicants note with appreciation that various past objections and rejections have been withdrawn, as stated on pages 3 to 5 of the Office Action.

Objection to the Specification

The Office Action objected to the specification for the use of the trademark "CY" without proper indication. Applicants have amended the specification to capitalize the term and include a TM designation, as well as include the generic terminology where appropriate. Withdrawal of this objection is respectfully requested.

35 U.S.C. § 103

The Office rejected claims 1, 2, 5, 11, 12, 16, 20, and 25 as allegedly obvious over Webb et al. (WO 97/46256; "Webb") in view of Rhode et al. (U.S. Patent No. 6,232,445; "Rhode") and Lehmann et al. (U.S. Patent No. 5,939,281; "Lehmann"). Applicants traverse this rejection for the following reasons.

As a preliminary matter, to more clearly point out the claimed subject matter, applicants have amended the claims to recite an array having, *inter alia*, a plurality of spatially-distinct areas that are configured to allow contact with one sample at essentially the same time and with the same sample. Applicants submit that the cited references, individually or in combination, fail to suggest such an array.

Applicants' array, as described in the specification (e.g., at page 13, lines 13-19) comprises a flat substrate or essentially flat substrate, e.g., a glass slide, that allows multiple spatially-distinct areas on the array to be in contact with the same sample at essentially the same time. Such an array has multiple advantageous, including the ability to investigate a plurality of potential T-cell epitopes (e.g., those immobilized on the spatially-distinct areas) in parallel using a single small volume of medium containing T cells and without the need for complex microfluidic systems.

According to the Office Action (at pages 7-10):

> Webb et al. teaches an array (see entire document) comprising a substrate (support, p49, lines 7-18) and a plurality of MHC molecules complexed with antigen derived peptides (p18, lines 9-17 and p50, line 1-p51, line 25) immobilized in spatially distinct areas on the substrate (wells of microtiter plates, p80, lines 24-31) ... Rhode et al. further teaches that an array of MHC complexes can be formed on a substrate such as 96-well plates (column 55, lines 45-51) ... Lehmann et al. teaches a method of detecting secreted cytokines by activated T-cells using cytokine capture assay (see entire document, particularly, column 3, lines 14-36) ... Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ plurality of different MHC-peptide complexes of Rhode et al., which are formed by a MHC molecule complexed with a library of different peptides, in the array of Webb et al. in order to screen T cells expressing a desired target structure in vitro.

As acknowledged in the Office Action (at page 8), Webb discloses immobilizing MHC class II molecules to wells of microtiter plates. The Office appears to equate each well to applicants' claimed spatially distinct area (see Office Action at page 8). Even so construed, skilled practitioners would readily appreciate that a microtiter plate is not a flat substrate. Skilled practitioners would also appreciate that there is no fluid communication between the wells of a microtiter plate to allow multiple wells to be in contact with one sample at essentially the same time and with the same sample, as required by the instant claims. Thus, Webb fails to suggest the claimed array.

Rhode fails to rectify the deficiencies of Webb. Like Webb, Rhode discloses using 96-well microtiter plates (as noted in the Office Action at page 9).

Neither does Lehmann remedy these deficiencies. Lehmann also discloses using microtiter plates (see, e.g., column 6, lines 15-17; and column 21, lines 17-20).

In the telephone interview, applicants' representative pointed to various claim language that is not present in any of the cited references, such as the language "a plurality of said spatially-distinct areas are configured to allow contact with one sample at essentially the same time and with the same sample." However, the Examiner was of the view that this claim language was not considered in the patentability analysis, because, according to the Examiner, this claim language was merely "functional" rather than "structural."

Applicants respectfully point out that, as MPEP 2173.05(g) states: "In a claim that was directed to a kit of component parts capable of being assembled, the Court held that limitations such as 'members adapted to be positioned' and 'portions . . . being resiliently dilatable whereby said housing may be slidably positioned' serve to precisely define present structural attributes of interrelated component parts of the claimed assembly. *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976)(emphasis added)." Likewise, applicants submit that the phrase "configured to allow contact with one sample at essentially the same time and with the same sample" (emphasis added) defines a structural attribute of the claimed array.

Accordingly, these references, individually or combined, do not teach every element of the claims, and even if combined as the Office suggests, do not provide the claimed invention. Since none of the references suggests an array having a flat substrate and a plurality of spatially-distinct areas that are configured to allow contact with one sample at essentially the same time and with the same sample, skilled practitioners, reading these references, would not have been led to applicants' array. The Office, therefore, has failed to establish a *prima facie* case of obviousness.

Even assuming that a *prima facie* case of obviousness could be established, applicants present surprising results sufficient to overcome such a case. As noted in applicants' reply to the previous Office Action, one of skill in the art at the time of the invention would not have expected that applicants' array would work. This is primarily because the factors secreted by the activated T cells are, by their very nature, soluble. These factors are for the most part small proteins and would be expected to diffuse readily through the medium. Such solubility is generally required for these factors to perform their functions in cell signaling and intercellular communication. Diffusion is clearly not an issue in microtiter plates, as each micro-well is an isolated assay chamber with homogeneous assay conditions. Any factors secreted by activated T

cells in the sample in one well are confined to that well. In addition, those of skill in the art take great pains to ensure and maintain this expected separation of materials in each well – hence the push towards microfluidics to allow access the separate micro-wells to enable fluids to be added and removed from individual micro-wells.

Applicants have taken an entirely different approach to eliminate the need for elaborate microfluidic systems and the need to add and remove fluids from individual micro-wells. Thus, although skilled practitioners would have expected diffusion to be a serious obstacle to applicants' presently claimed array system, applicants surprisingly discovered that diffusion is not a problem, and that accurate results can still be read, even though multiple spatially-distinct areas are all contacted with the same sample at essentially the same time.

Skilled practitioners would have expected diffusion to be a problem for several reasons. First of all, the size of a typical array element is very small. For example, the present application at page 14, lines 12-16, suggests a size of about 50 microns, and Figure 2A shows multiple spots within a 240 micron wide area. That is, factors secreted by T cells stimulated by a particular MHC-peptide complex immobilized in one area would be expected to diffuse through the media away from that area, and to another area with a different immobilized MHC-peptide complex. Accordingly, skilled practitioners would have expected that using applicants' array would result in the signals being lost, compromised, or degraded, such that faint signals (e.g., from low number responders) or distinct signals (e.g., from a single area of MHC-peptide complexes) would not be detectable. Examples 2 and 3 of the present application demonstrate that this is not the case. However, prior to the present invention skilled practitioners reading the cited prior art would not have had a reasonable expectation that the applicants' claimed array would produce useful results.

Therefore, as Webb, Rhode, and Lehmann fail to suggest every element recited in the instant claims, and the combination suggested in the Office does not provide the claimed invention, the Office has failed to establish a *prima facie* case of obviousness. Further, the unexpected operability and effectiveness of the claimed arrays as disclosed in the specification and examples are sufficient to overcome any alleged *prima facie* case of obviousness, if indeed such could be established. Thus, applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office also rejected claims 3, 4, 6, and 7 as allegedly obvious over Webb in view of Rhode, Lehmann, and Taylor (U.S. Patent No. 6,103,479). Applicants traverse this rejection for the following reasons.

The Office Action states (at pages 10-12):

> Webb et al. in view of Rhode et al. and Lehmann et al. fails to teach an array, wherein the spatially distinct areas are all surrounded by a single hydrophobic barrier ... it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the substrate (glass or silicon) of Taylor, which includes all the spatially-distinct areas surrounded by a single hydrophobic barrier and having either one type of compounds (the same MHC molecules) or a combinatorial of distinct compounds (different MHC molecules) in the array of Webb et al. in view of Rhode et al. and Lehmann et al. in order to conduct simultaneous analysis of multiple types of cell interactions.

Claims 3, 4, 6 and 7 all depend from claim 1, so are patentable for at least the reasons set forth above. The deficiencies of Webb, Rhode, and Lehmann are discussed above. Taylor fails to rectify these deficiencies, because it does not suggest an array having a plurality of spatially-distinct areas configured to allow contact with one sample at essentially the same time and with the same sample. In fact, Taylor teaches away from such an array. Taylor describes a non-uniform micro-patterned array hydrophilic spots that Taylor refers to as "wells" (see, e.g., column 8, lines 35-37). As shown in FIGs. 1A and 1B, for example, each "well" is surrounded by a hydrophobic material that isolates each "well" from all the other "wells." Taylor also describes a microfluidic delivery system that has a multitude of individual microfluidic channels, each of which delivers fluid to an individual well (see, e.g., column 13, line 57 to column 14, line 43; and Figs. 4, 5 and 10). That is, the wells in Taylor's array are designed to receive separate samples, rather than be in contact with one single sample.

As described in Example 2 of Taylor, such a microfluidic delivery system was used to deliver an array of compounds to an array of wells each containing cells, to determine which compound induced a specific response in these cells. Thus, each test compound was delivered to an individual well, and was kept separate from each other compound. Skilled practitioners would have reasonably concluded that the array described in Taylor is more like a microtiter plate, in which each well is a separate assay chamber. Thus, reading Taylor, skilled practitioners

would have been led away from applicants' array, in which multiple spatially-distinct areas are configured to allow contact with one sample, for example, by being surrounded, as a group, by one hydrophobic or other barrier, rather than having each location be surrounded by its own barrier as in Taylor.

As Webb, Rhode, Lehmann, and Taylor, either singly or in combination, fail to disclose the claimed array, and Taylor teaches away from the array, applicants submit that claims 3, 4, 6 and 7 are not obvious in view of these references. Withdrawal and reconsideration of this rejection are respectfully requested.

The Office also rejected claims 8 and 9 as allegedly obvious over Webb, Rhode, Lehmann, and Tom-Moy et al. (U.S. Patent No. 6,235,488, "Tom-Moy"). Applicants disagree. As claims 8 and 9 depend from claim 1, they are patentable for at least the same reasons. Tom-Moy also does not suggest an array having a plurality of spatially-distinct areas configured to allow contact with one sample at essentially the same time with the same sample. The Office Action (at page 12) cites Tom-Moy only for disclosing the substitution of streptavidin for avidin, and Tom-Moy fails to provide any other relevant information. Thus, Tom-Moy fails to remedy the deficiencies of Webb, Rhode and Lehmann. Accordingly, claims 8 and 9 are not obvious over these references, individually or combined. Applicants respectfully request withdrawal of this rejection.

The Office also rejected claim 13 allegedly obvious over Webb, Rhode, Lehmann, Abraham et al. (J. Immunol., 20014, Vol. 167, pp5193-5201; "Abraham"), and Mikesell et al. (U.S. Published Patent Application No. US 2002/0095024, "Mikesell"). Applicants do not agree. Claim 13 depends from claim 1, and is patentable for at least the same reasons discussed above. The Office Action (at page 14) cites Abraham and Mikesell for disclosing the use of anti-CD11a antibodies as costimulatory antibodies. These references do not suggest applicants' array and, therefore, fail to rectify the deficiencies of Webb, Rhode and Lehmann. Thus, claim 13 is not obvious over these references, individually or in combination. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants request that all claims be allowed. The $60 fee for a one-month extension and the $405 fee for an RCE are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-212001.

Respectfully submitted,

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